Risk Factors for Mortality in Patients with *Stenotrophomonas maltophilia* Bloodstream Infections in Immunocompetent Patients

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ABSTRACT

Objective: This study aimed to evaluate bloodstream infections caused by *Stenotrophomonas maltophilia* in immunocompetent patients with respect to clinical features and risk factors for mortality.

Methods: We reviewed bloodstream infections detected between January 1, 2012, and July 1, 2021, to identify nosocomial *S. maltophilia* bacteremia in Koşuyolu Research and Training Hospital.

Results: We identified a total of 97 patients with *S. maltophilia* bloodstream infections. Of these, 17 patients were excluded because of community-acquired infections (n=9), contamination with *S. maltophilia* (n=3), and insufficient data (n=5), with 80 (57.5% males) patients remaining for analysis. The source of infection was the respiratory tract in 28 (35%) patients. A central venous catheter was used in 60 (75%) patients, which required replacement in 23 patients within five days after detecting *S. maltophilia* bacteremia. On antimicrobial susceptibility testing, 71 strains were found to be susceptible and 9 (11.3%) resistant to trimethoprim-sulfamethoxazole. Thirty-day mortality was 33.8%. Non-survivors differed significantly from survivors with respect to higher rates of central venous catheters (*p*=0.020), mechanical ventilation (*p*=0.006), urinary catheters (*p*=0.021), septic shock (*p*=0.001), hypoalbuminemia (*p*=0.026) and thrombocytopenia (*p*=0.039). *S. maltophilia* bacteremia was independently associated with mortality in patients with hypoalbuminemia, and replacement of central venous catheters had a protective role in reducing mortality.

Conclusion: As with other bacterial infections, *S. maltophilia* bacteremia is associated with a considerably high mortality rate in patients with cardiac conditions. The replacement of the catheter seems to play a beneficial role in 30-day survival.

Keywords: *Stenotrophomonas maltophilia*, bloodstream infections, mortality

INTRODUCTION

*S*tenotrophomonas maltophilia is a Gram-negative, non-fermentative aerobic bacterium that infects patients, especially with severe comorbidities such as hematological malignances. It is commonly found in the environment and hospital settings. The most common clinical presentations are pneumonia and bloodstream infections (1, 2).

S. maltophilia is known to have intrinsic resistance mechanisms to many antibiotic classes, including carbapenems, aminoglycosides, most third-generation cephalosporins, and other β-lactams, making it difficult to determine the appropriate antibiotic treatment (1, 2). For example, although trimethoprim-sulfamethoxazole (TMP-SMX) is the first-line treatment, resistance to this drug has been reported at a rate of 2.1-47.1% in different reports (2-8).

S. maltophilia-associated mortality rates vary widely from 16 to 69% in the literature, depending on the coexisting conditions (1, 4-6, 8-13). The majority of studies have been conducted on patients with hematological malignancies or pediatric patients. Therefore, we evaluated bloodstream infections caused by *S. maltophilia* in immunocompetent patients with respect to clinical features and risk factors for mortality.

MATERIALS AND METHODS
Hospital Settings
This retrospective study was performed in Koşuyolu Research and Training Hospital, a 465-bed tertiary referral center in İstanbul, Turkey, with three intensive care units (ICU) (adult cardiovascular surgical ICU, pediatric cardiovascular surgical ICU, coronary ICU) as well as cardiovascular surgery clinics (one for pediatric cardiovascular surgery), gastroenterology surgery clinic, transplantation clinic, and cardiology clinics.

The institutional review board of Koşuyolu Research and Training Hospital approved the study on January 12, 2022, with the decision number of 2022/530.

Patients
We reviewed bloodstream infections detected between January 1, 2012, and July 1, 2021, to identify nosocomial S. *maltophilia* bacteremia. Patients who were 16 years of age or older and had complete hospital data were included. Those who had community-acquired bloodstream infections were excluded.

Data Retrieval
Electronic medical records and infectious diseases charts were searched for patients' demographic data, comorbidities, history of ICU admission, hospital setting at the time of detection of bacteremia, antibiotic therapies prior to and after the detection of bacteremia, presence of central venous or urinary tract catheters and mechanical ventilation support and development of septic shock. Acute Physiology and Chronic Health Evaluation (APACHE) II scores were calculated in ICU patients during the detection of S. *maltophilia* bacteremia (SMB).

Microbiological Testing
Blood samples were cultured using the BACT/ALERT® 3D automated microbial detection system (bioMérieux, Marcy-l'Étoile, France). All clinical isolates were identified, and susceptibility to TMP-SMX was determined using the automated VITEK® 2 Compact system that utilizes GN ID cards (bioMérieux, Marcy-l'Étoile, France). Results were interpreted according to the identification criteria set for S. *maltophilia* by the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

Definitions
Nosocomial SMB was defined as the detection of S. *maltophilia* in blood samples obtained at least 48

HIGHLIGHTS

- *Stenotrophomonas maltophilia* bacteremia is of concern not only in patients with malignancies but also in critically ill patients with several comorbidities with a high mortality rate.

- Thirty-day mortality was 33.8% in *S. maltophilia* bacteremia.

- The replacement of the central venous catheter seems to play a beneficial role in 30-day survival.

- *S. maltophilia* bacteremia was independently associated with mortality in patients with hypoalbuminemia.

hours after admission due to clinical symptoms. Contamination with S. maltophilia was defined as patients who had no symptoms of systemic infection and had no growth in the control blood cultures performed without initiation of antibacterial therapy active against S. maltophilia. The source of bacteremia was determined according to the Centers for Disease Control and Prevention (CDC) definitions (14). Simultaneous detection of bacteremia because of other pathogens before or after 24 hours of the identification of S. *maltophilia* was defined as polymicrobial bacteremia. Septic shock was defined by the presence of sepsis complicated by persistent hypotension requiring vasopressor agents to maintain a mean arterial pressure of 65 mm Hg (15).

Thrombocytopenia was defined as a platelet count of less than 150,000/mL and hypoalbuminemia as an albumin level of less than 3g/dL at the time of bacteremia. Appropriate empirical antibiotic therapy was defined as the administration of an antimicrobial agent initiated intravenously and in an appropriate dosage (TMP-SMX, 15 mg/kg/day based on TMP component) within 24 hours of the onset of S. *maltophilia* bacteremia and was shown to be effective against S. *maltophilia* isolates grown in blood cultures. Appropriate definitive antibiotic therapy was defined as initiating an antimicrobial agent intravenously and in an appropriate dosage (TMP-SMX, 15 mg/kg/day based on TMP component) based on positive cultures and susceptibility results. The replacement of the central venous catheter (CVC) was defined as the procedure performed no later than five days after the onset of bacteremia. Mortality was defined as death occurring within 30 days after the detection of SMB.

Statistical Analysis

The statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) 25.0 (IBM Corp., Armonk, NY, USA). Demographic, clinical, and laboratory data of the non-survival and the survival groups were compared. Continuous variables were expressed as means (standard deviation, SD), and categorical variables were expressed as numbers (percentage). The Kolmogorov-Smirnov test was used to analyze the normality of the distribution of parameters. Data that did not show a nor-

mal distribution were expressed as a median with the interquartile range (IQR). The nonparametric Mann-Whitney U-test was used to compare numerical data, and the chi-squared test or Fisher's exact test was used to compare categorical data.

The effects of variables on mortality were evaluated using univariate (Kaplan–Meier) and multivariate analyses. All variables with a *p-value* of less than 0.05 in the univariate analyses were included in the multivariate analyses. Cox regression analysis was performed to evaluate the factors associated with 30-day mortality. A *p-value* of less than 0.05 was considered significant.

RESULTS
Demographic and Clinical Characteristics of the Patients

We identified a total of 97 patients with SMB. Of these, 17 patients were excluded because of community-acquired infections (n=9), contamination with S. *maltophilia* (n=3), and insufficient data (n=5), with 80 (57.5% males) patients remaining for analysis. The mean age was 54.9±16.5 (ranges: 16-87) years, and 23 patients were older than 65 years of age. The most common comorbid diseases were hypertension (55%), followed by diabetes mellitus (42.5%), and congestive heart failure (27.5%). Seventy-one patients had a history of ICU admission either before or after the detection of bacteremia. The median length of hospitalization was 60 (IQR 28-101) days, and the median duration of hospitalization before identification of S. *maltophilia* was 28.5 (IQR 16.3-51.3) days (Table 1).

At the time of diagnosis of SMB, 54 patients had a fever (≥ 38 °C), nine had hypothermia, 22 had respiratory symptoms, and 22 were in septic shock (Table 1). The majority of patients (n=58) had been receiving antimicrobial therapy before the identification of S. *maltophilia* (Table 1).

Thirteen patients had polymicrobial infections caused by *Enterococcus* spp. (n=4), *Acinetobacter baumannii* (n=3), *Klebsiella pneumoniae* (n=2), *Candida* spp. (n=2), *Sphingomonas paucimobilis* (n=1) and methicillin-resistant coagulase-negative staphylococci (n=1).

Table 1. Overall demographic and clinical characteristics of patients with S. *maltophilia* bacteremia.

Factors	Total n=80 (%)	Non-survivors n=27 (%)	Survivors n=53 (%)	p
Age, y, mean ± SD	54.9±16.5	57.3±15.3	53.7±17.1	0.3
Male	46 (57.5)	17 (63)	29 (54.7)	0.4
Comorbidities				
Hypertension	44 (55)	12 (44.4)	32 (60.4)	0.18
Diabetes mellitus	34 (42.5)	11 (40.7)	23 (43.4)	0.82
Congestive heart failure	22 (27.5)	8 (29.6)	14 (26.4)	0.76
Cronic kidney disease	18 (22.5)	6 (22.2)	12 (22.6)	0.97
Coronary artery disease	14 (17.5)	4 (14.8)	10 (18.9)	0.65
Chronic obstructive pulmonary disease	7 (8.8)	1 (3.7)	6 (11.3)	0.25
Source of bacteremia				
Bloodstream infection	52 (65)	21 (77.8)	31 (58.5)	0.144
Respiratory tract infection	28 (35)	6 (22.2)	22 (41.5)	0.144
Prior hospital stay (days), median (IQR)	28.5 (16.3-51.3)	24 (18-49)	29 (15.5-54)	0.88
Antibiotic treatment in past month	58 (72.5)	22 (81.5)	36 (67.9)	0.308
A history of hospitalization of the ICU	71 (88.8)	27 (100)	44 (83)	**0.025**
Central venous catheter	60 (75)	25 (92.6)	35 (66)	**0.02**
Replacement of central venous catheters *	23 (23.6)	3 (12%)	20 (57.1)	0.001
Hemodialysis catheter	24 (30)	11 (40.7)	13 (24.5)	0.216
Mechanical ventilation	57 (71.3)	25 (92.6)	32 (60.4)	**0.006**
Urinary catheter	64 (80)	26 (96.3)	38 (71.7)	0.021
Extracorporeal membrane oxygenation	26 (32.5)	7 (25.9)	19 (35.8)	0.52
Total parenteral nutrition	16 (20)	9 (33.3)	7 (13.2)	0.067
Surgery (within 30 days)	24 (30)	10 (37)	14 (26.4)	0.47
Polymicrobial bacteremia	13 (16.3)	5 (18.5)	8 (15.1)	0.9
TMP-SMX resistance	9 (11.2)	5 (18.5)	4 (7.5)	0.157
APACHE II score, median (IQR)	16 (10.8-24.3)	24.5 (21.8-26)	12 (8-16)	0.001
APACHE II score > 20	28 (35)	23(85.2)	5 (9.4)	0.001
Clinical features				
Temperature > 39 °C	54	17	37	0.714
Hypothermia	9 (11.3)	3 (11)	6 (11.3)	0.055
Respiratory symptoms	22	16	6	0.624
Septic shock	22 (27.5)	17 (63)	5 (9.4)	0.001
Appropriate empirical antibiotic therapy	11 (13.8)	3 (11.1)	8 (15.1)	0.74
Appropriate definitive antibiotic therapy	60 (75)	18 (66.7)	42 (79.2)	0.339

Continue to Table 1

No antibiotic use	8 (10)	5 (18.5)	3 (5.7)	0.112
Thrombocytopenia	36 (45)	17 (63)	19 (35.8)	0.039
Hypoalbuminemia	57 (71.3)	24 (88.9)	33 (62.3)	0.026
Procalcitonin median, (IQR)	1.1 (0.3-3.6)	1.8 (0.7-11.8)	0.5 (0.2-1.2)	0.002
Procalcitonin >1ng/mL (n=62)	18 (29)	12 (50)	6 (15.8)	0.009

SD: Standard deviation, **IQR:** Interquartile range, **ICU:** Intensive Care Unit, **TMP-SMX:** Trimethoprim sulfamethoxazole, **APACHE:** Acute Physiology and Chronic Health Evaluation, * All 60 patients had central venous catheters

Table 2. Univariate and multivariate analysis of risk factors associated with 30-day mortality in patients with S. *maltophilia* bacteremia.

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*	OR	95% CI	*p*
A history of hospitalization of the ICU	0.83	0.735-0.938	0.073			
Central venous catheter	6.429	1.367-30.24	0.086			
Replacement of central venous catheter	0.102	0.26-0.406	<0.001	0.219	0.094-0.507	0.001
Mechanical ventilation	8.203	1.755-38.336	0.026			
Urinary catheter	10.263	1.276-82.546	0.046			
APACHE II score >20	53.667	11.679-246.6	<0.001			
Septic shock	16.32	4.878-54.601	<0.001			
Thrombocytopenia	3.042	1.163-7.96	0.03			
Hypoalbuminemi	4.848	1.292-18.196	0.011	5.367	1.456-19.781	0.012
Procalcitonin >1	5.333	1.633-17.416	0.008			

OR: Odds Ratio, **CI:** Confidence interval, **APACHE:** Acute Physiology and Chronic Health Evaluation

Source of Infection

The source of infection was the respiratory tract in 28 (35%) patients. A CVC was used in 60 (75%) patients, which required replacement in 23 patients within five days after detecting SMB (Table 1).

### In Vitro Antimicrobial Susceptibility

On antimicrobial susceptibility testing, 71 strains were susceptible, and nine were resistant to TMP-SMX (11.3%) (Table 1).

Risk Factors Associated with 30-Day Mortality

Thirty-day mortality was 33.8%. Non-survivors differed significantly from survivors with respect to higher rates of CVCs (*p*=0.020), mechanical ventilation (*p*=0.006), urinary catheters (*p*=0.021), septic shock (*p*=0.001), hypoalbuminemia (*p*=0.026) and thrombocytopenia (*p*=0.039). The median APACHE II scores were 24.5 and 12 in the non-survivor and survivor groups, respectively (*p*<0.001). The incidence of an APACHE II score of >20 was remarkably higher among non-survivors as compared with survivors (85.2% vs 9.4%, *p*=0.001) as well as the incidence of a procalcitonin level of >1 ng/mL (50.0% vs 15.8%, *p*=0.009). The incidence of catheter replacement was also higher among survivors (*p*=0.001) (Table 1).

Tablo 2 summarizes the results of univariate and multivariate analyses for 30-day mortality. Eight variables were found to be significantly associated with mortality in univariate analysis. In multivari-
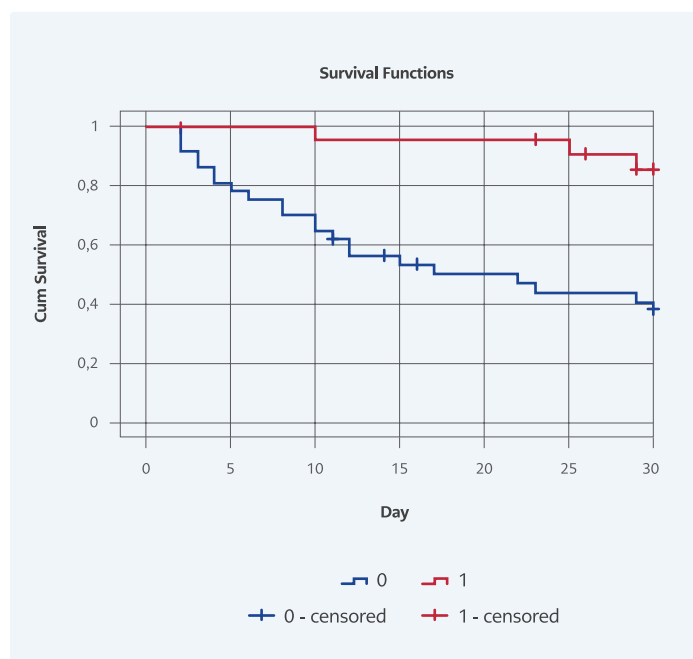
Figure 1. Effect of CVC replacement on survival (*p*=0.001).

ate analysis, only two variables were independently associated with mortality, including hypoalbuminemia and replacement of CVCs. The Kaplan-Meier curve was plotted to estimate the effect of replacement of CVC on survival (Fig. 1). Significantly higher in patients with CVC replacement survival rates compared to those without catheters replacement.

DISCUSSION

Our results showed that *S. maltophilia* bacteremia was independently associated with mortality in patients with hypoalbuminemia, and replacement of CVCs had a protective role in reducing mortality. The majority of studies on the risk factors of *S. maltophilia*-associated mortality were performed in patients with hematological malignancies or the pediatric age group. The present study differs in this respect in that all the participants were hospitalized for cardiac causes, and none had hematological malignancies or were in the pediatric age group.

S. maltophilia-associated mortality rates vary widely from 16 to 69% in the literature, depending on the coexisting conditions (1, 4-6, 8, 10-13). In the present study, 30-day mortality among patients with cardiac conditions was 33.8%.

Understandably, the removal or replacement of CVCs would have a beneficial role in mortality because CVCs represent a suitable environment for biofilm formation (13). In line with previous studies addressing the preventive role of CVC removal (6, 8, 12), the rate of CVC replacement was significantly higher among survivors than among non-survivors (Table 1).

Hypoalbuminemia represents a complicating factor in the setting of SMB infections and adversely affects survival (13). In the current study, the incidence of hypoalbuminemia was significantly higher among non-survivors than among survivors (88.9% vs. 62.3%). It is known that hypoalbuminemia is often observed in patients with sepsis; it may increase the risk of infections and mortality in critically ill patients. Moreover, albumin is a negative acute phase reactant. However, the causal relation is not known despite such an association (16).

Appropriately empirical antibiotic use remains challenging in the presence of suspected bacterial infections, particularly for *S. maltophilia*. Inappropriate empirical antimicrobial treatment was reported to be an independent risk factor for mortality in *S. maltophilia* infections (5, 10). Conversely, the appropriateness of either empirical (8, 12) or definitive (12) antimicrobial therapy has been reported to be unrelated to mortality. In the current study, the rate of empirical antibiotic therapy with TMP-SMX might be beyond expectations, possibly owing to an increased awareness of *S. maltophilia* infections at our institution, particularly heightened by the emergence of an *S. maltophilia* outbreak recently reported by the authors (17). Our findings showed that the survivor and non-survivor groups did not differ significantly with respect to the use of either appropriate empirical or definitive antibiotic therapy (Table 1).

The retrospective study design and relatively small patient size are the main limitations of the present study.

In conclusion, as with other bacterial infections, *S. maltophilia* bacteremia is associated with a considerably high mortality rate in patients with cardiac conditions. Hypoalbuminemia is associated with mortality. The catheter replacement seems to play a beneficial role in 30-day survival.

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